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U.S. EPA HIGH PRODUCTION VOLUME  
CHEMICAL VOLUNTARY TESTING PROGRAM

CATEGORY JUSTIFICATION  
AND  
TEST PLAN

ETHYLPHENOL ISOMERS

Submitted by:  
MERISOL USA LLC  
Houston, Texas

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## INTRODUCTION

### Ethylphenols

Ethylphenols are liquids or crystals recovered from petroleum streams, coal coking operations and coal gasification. There are three isomeric forms of ethylphenol: o-, m-, and p-ethylphenol. The boiling points for o-, m-, and p-ethylphenol are 204.6°C, 218.0°C and 218.4°C, respectively.

### Merisol's Process

Merisol's phenolic products are highly versatile materials that are used as intermediates in the manufacture of a wide variety of industrial products such as resins, flame retardants, antioxidants, and insulating varnishes. Merisol production of phenolics is essentially a recovery, purification, and fractionation operation. Merisol feedstocks are generally secondary streams from refineries, coal coking operations and coal gasification. From these feedstocks a multi-component phenolic mixture called "crude cresylic acid" is produced, which is composed of phenol, cresols, xyenols, ethylphenols, and, to a lesser extent, other higher boiling alkyl phenols. This mixture is processed to remove impurities, and then separated into various fractions by distillation. Distillation produces phenol, o-cresol, m- and p-cresol mixture, and fractions containing varying compositions of xyenols, ethylphenols, and higher boiling alkyl phenols. Merisol also has a proprietary process that produces p-cresol and m-cresol from the m-cresol and p-cresol mixture produced by distillation. Because of similarities in boiling points of components in the starting phenolic mixture, isolation of all pure m- and p-ethylphenol isomers by distillation is not possible.<sup>1</sup> Isolation of the o-ethylphenol isomer by distillation is possible, but has not proved to be commercially viable.

### Exposure Pattern for the Ethylphenols

Merisol sells pure phenol, o-cresol, m-cresol and p-cresol. These are also sold in blends, as are the mixtures of ethylphenols and xyenols. Merisol produces and sells ethylphenols contained in mixtures and does not sell or distribute any isomer of these as isolated materials in HPV threshold quantities. Therefore, public (and employee) exposure, as well as potential environmental exposures to Merisol's products, are only to blends and mixtures containing ethylphenols. Because these Merisol products are generally moved into commerce as starting materials for further chemical processing, there is little consumer exposure to ethylphenols. Merisol is by far the major, if not sole, U.S. producer of ethylphenols.<sup>2</sup>

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<sup>1</sup> For the same reason, as discussed in Merisol's concurrently submitted proposal for mixed xylenols, isolation of all pure xylene isomers by distillation is not possible.

<sup>2</sup> Merisol understands that in the past, another company may have imported amounts of up to 600,000 pounds per year of pure p-ethylphenol that were used as an intermediate in producing another substance; however, this activity may no longer take place. Merisol also understands that another company may be using amounts up to 20,000 pounds per year of pure m-ethylphenol. Merisol has no information concerning, or basis to believe there is, any current production or importation of pure o-ethylphenol.

Merisol is a custom blender of phenolics. The number of different phenolic mixtures Merisol typically produces in a year is approximately 50, but can go as high as 100. These mixtures contain varying compositions of phenol, cresols, xylenols, ethylphenols, and higher boiling alkyl phenols. Ethylphenols, as well as xylenols, phenol, and cresols, are not components of every Merisol product mixture.

A breakdown of numbers of ethylphenol isomers contained in product mixtures is given in Text Table 1. Table 1 illustrates that Merisol products containing virtually all of the ethylphenol produced by Merisol are sold in products containing at least two of the three ethylphenol isomers.

Table 1: Distribution of Individual Ethylphenol Isomers  
In Merisol Products

	Number of Different Ethylphenol Isomers Present as Components in Merisol Products		
	1 ethylphenol isomer in product	2 ethylphenol isomers in product	3 ethylphenol isomers in product
% of total ethylphenol placed into commerce by Merisol	0.6	42.3	57.1

## DESCRIPTION OF THE CATEGORY

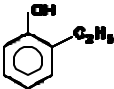
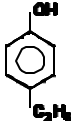
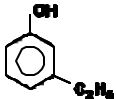
### Ethylphenols

Ethylphenols are liquids or crystals recovered from petroleum streams, coal coking operations, and coal gasification. There are three isomeric forms of ethylphenol: o-, m-, and p-ethylphenol. Each of these isomers appear in the EPA HPV list of chemicals to be evaluated. Identification of the isomers appears in Text Table 2, below. For purposes of the Ethylphenols Category, Merisol is defining ethylphenols as a mixture containing equal portions of:

o-ethylphenol (CAS # 90006)  
p-ethylphenol (CAS# 123079)  
m-ethylphenol (CAS# 620177).

This mixture is intended to represent the Category “Ethylphenols” for HPV data development, as well as each separate ethylphenol isomer. Each isomer is represented in the Category. Data developed on this Category are intended to represent all mixtures of ethylphenol, as well as the individual ethylphenol isomers.

Table 2 Ethylphenols – Chemical Name, CAS Number, and Structure

Chemical	o-Ethylphenol	p-Ethylphenol	m-Ethylphenol
CAS Registry Number	90006	123079	620177
Molecular Structure			

## CATEGORY JUSTIFICATION

### ETHYLPHENOLS

As structural isomers, the members of the Ethylphenols Category share the same molecular weight, or in the case of the mixture, average molecular weight. The substituent groups on the phenolic ring are always ethyl groups, so branching differences among the side groups is not a possibility in this Category. Examination of the physical-chemical properties for each isomer (Text Table 3) shows that the physical-chemical properties of the isomers are quite similar, due to the structural similarities. Of particular importance to environmental effects and potential human health effects are the values for octanol/water partition coefficient and water solubility. The values for octanol/water partition coefficient are 2.40 to 2.58 for each of the ethylphenol isomers. Ethylphenols appear to be relatively water soluble: the water solubility value at 25°C for p-ethylphenol is 4900 mg/L and for o-ethylphenol, 5340 mg/L. These values suggest that ethylphenol isomers and mixtures of isomers will distribute similarly in the environment and have similar residence times in environmental compartments. Bioaccumulation attributes will be similar among the isomers and the mixture also. Vapor pressures of the isomers at 25°C range from 0.050 to 0.153 mmHg for the ethylphenols, also supporting a similar pattern of airborne distribution. Individually and as a group the ethylphenols are expected to exhibit low-to-moderate mobility in soil based on the  $K_{ow}$  values. Hydrolysis values have not been reported for ethylphenols, presumably due to the absence of a hydrolyzable functional group. Within the family of ethylphenol isomers, the physicochemical properties are expected to manifest similar effects on the environment and potentially on human health.

The biological response patterns of ethylphenols, like the physicochemical properties, derive from the structural similarities of the isomers. There are data from independent sources to support this position by way of example or illustration. For instance, in work completed by the National Toxicology Program (NTP) with a group of structurally-related isomers, in this case methyl phenols, or cresols, toxicology studies showed that there was no one predominantly toxic isomer and that target organs for toxicity and toxic effect dose levels were relatively consistent across the isomers. This is expected to be the case for ethylphenols.

Table 3: Ethylphenols Physical Properties

Chemical	o-Ethylphenol	p-Ethylphenol	m-Ethylphenol
CAS Registry Number	90006	123079	620177
Boiling Point	204.6°C	218.0°C	218.4°C
Melting Point	18°C	-4°C	46°C
Density	1.014 @ 25°C	1.028 @ 20°C	1.011 @ 20°C
Oil/Water Partition Coefficient	2.47	2.58	2.40
Water Solubility	5340 mg/L @ 25°C	4900 mg/L @ 25°C	Slightly soluble
Vapor Pressure	0.153 mmHg@ 25°C	0.089 mmHg@ 25°C	0.050 mmHg@ 25°C
K <sub>o/w</sub>	530	480	600
Photodegradation in Air	T <sub>1/2</sub> = 9 hrs.	T <sub>1/2</sub> = 5 hrs.	T <sub>1/2</sub> = 9 hrs.

#### Toxicological Justification for the Ethylphenols Category

Ethylphenols are closely structurally related to methyl phenols, which are also known as cresols. The toxicological justification for the Ethylphenols Category is that existing studies of methyl phenols have demonstrated that the methyl phenol isomers are remarkably equivalent in toxicity and that binary and tertiary mixtures of cresol isomers do not produce toxic interactions among the isomers, *i.e.*, that mixtures of cresol isomers do not exhibit more than additive toxicity.<sup>3</sup> Attachment 1 to this document presents in tabular form summaries of developmental

<sup>3</sup> In 28-day feeding studies conducted on cresol isomers by the NTP, mice and rats were treated with equivalent dose levels of each isomer and in 90-day studies rats received equivalent doses of ortho-cresol or the meta/para-mix. The author of the study, Dennis Dietz, observed so little difference among the cresol isomers in toxicity (both concentration and dose effects) that he chose to summarize the results of the 28- and 90-day studies together. In summarizing the subchronic toxicity of cresol isomers, Dietz said:

The cresol isomers exhibited a generally similar pattern of toxicities in rats and mice. Dietary concentrations of 3,000 ppm appeared to be minimal effect levels for increases in liver and kidney weights and 15,000 ppm for deficits in liver function. Histopathologic changes, including bone marrow hypocellularity, irritation to the gastrointestinal tract and nasal epithelia, and atrophy of female reproductive organs, occasionally occurred at 10,000 ppm, but were more common at the high dose of 30,000 ppm (Ref. NTP, 1992).

In these studies, which included an assessment of individual isomers and an isomer mix, no evidence of toxic interaction was reported by the author, Dietz. In the final report of those studies, Dietz concluded that “In summary, the various cresol isomers exhibited a generally similar spectrum of toxicities in these studies, with few exceptions as noted previously. There was little evidence to suggest a significant increase in toxicity with longer exposures in the 13-week study when compared to the effects seen with similar doses in the 28-day study.”

and reproductive toxicity data, as well as genetic toxicity data on methyl phenol isomers. From inspection of the Attachment 1 tables, it can be seen that within a test animal species (rabbit or rat), methyl phenol (cresol) isomers exhibited similar or the same toxicity. Effective doses, expressed as NOAELs, remained constant or very close across isomers, never more than one dose level apart. Target organs for isomer toxicity and systemic toxic effects were nearly superimposable across isomers. This qualitative and quantitative comparability of toxicity across isomers exhibited in the cresols data set is consistent with cresol isomers results described by Dennis Deitz, cited in the footnote above. Genetic toxicity studies of the cresol isomers show few inconsistencies in test results across isomers. In the seven cases where there are data on a mixture of the isomers, as well as data on one or more isomers, there is no difference in results in those cases (two) where data are available on each isomer and the mixture. In another case, the positive assay result for the mixture can be attributed to a positive result for an isomer in the same test. In the remaining four examples, isomeric uniformity of genetic activity cannot be affirmed or refuted because of the incomplete data set.

The toxicological equivalence or near equivalence of methyl phenols (cresols) derives from the structural similarity shared by members of the group (isomeric forms of methyl phenol) and the similarity in chemical/physical properties which follows from the structural relationship. In an analogous manner, a complementary structure-activity relationship is anticipated with ethylphenols based on the structural similarity among this group of isomers. The demonstration of a structure-activity relationship among the methyl phenol isomers and the expectation of a parallel structure-activity relationship for the homolog ethylphenols is the toxicological justification of the Ethylphenols Category for HPV testing.

## CATEGORY TEST PLAN

Details for the toxicological work on ethylphenols are unavailable. Thus, while the existing mammalian and ecological toxicology data, when viewed as a whole, strongly support toxicology data development on an ethylphenol mixture as a category for HPV testing, the data may not in every case be adequately reported to be relied upon for HPV evaluations. Accordingly, Merisol proposes that no existing studies will be used to supply data for SIDS endpoints in the Ethylphenols Category. Merisol is not relying on data developed on analogous compounds to satisfy Ethylphenols Category testing but instead will develop data for each SIDS Screening Endpoint using the ethylphenol isomer mixture identified above and shown again below:

Merisol is defining ethylphenols as a mixture containing equal portions of:

o-ethylphenol (CAS # 90006)  
p-ethylphenol (CAS# 123079)  
m-ethylphenol (CAS# 620177).

This mixture is intended to represent the Category “Ethylphenols” for HPV data development, as well as each separate ethylphenol isomer. Data developed on this Category are intended to satisfy all requirements under the HPV Challenge Program for all mixtures of ethylphenols, as well as the individual ethylphenol isomers.

The HPV testing proposed by Merisol for the Ethylphenols Category is shown in Text Table 5.

## CONCLUSION

Ethylphenol mixtures sold or distributed in the U.S. by Merisol are of variable composition. Testing every possible variation would violate animal use goals without producing additional meaningful scientific information, and would thus also be unnecessarily burdensome. Because exposure of people and the environment is to mixtures of ethylphenols, data developed on a mixture of three ethylphenols will provide cogent and reliable information for assessment of the potential hazards its ethylphenol-containing products may present to humans and the environment. This approach to data development also will account for any interactions between ethylphenol isomers that may impact toxicity, although none are expected.

Merisol proposes a category approach for testing ethylphenols. The testing is to account for each of the ethylphenol listings on EPA's HPV list of chemicals to be tested.

Table 5: Ethylphenols Category HPV Test Plan

HPV DATA ENDPOINT	PROPOSED DATA DEVELOPMENT METHOD
1. CHEMISTRY	
Melting Point*	OECD Test Guideline 102
Boiling Point*	OECD Test Guideline 103
Vapor Pressure	OECD Test Guideline 104
Water Solubility	OECD Test Guideline 105
Partition Co-Efficient	OECD Test Guideline 107
2. ENVIRONMENTAL FATE	
Photodegradation	Estimate/model
Hydrolysis (Stability in Water)	OECD Test Guideline 111
Biodegradation	OECD Test Guideline 301
Fugacity	Fugacity Level III Modeling
3. HEALTH EFFECTS	
Acute Toxicity	Acute Oral Toxicity: OECD Health Effects Test Guideline 401**
Repeat Dose Toxicity	Combined Repeat-Dose Toxicity Study with Reproductive/Developmental Toxicity Screen: OECD Health Effects Test Guideline 422
Repro-Develop. Toxicity	
Genetic Toxicity	Bacterial Mutation Test: OECD Health Effects Test Guideline 471 Mammalian Erythrocyte Micronucleus Test: OECD Health Effects Test Guideline 474
4. ECOTOXICITY	
Fish	Acute Toxicity to Fish: OECD Test Guideline 203
Daphnia	Acute Toxicity to Aquatic Invertebrates: OECD Test Guideline 202
Algae	Acute Toxicity to Aquatic Plants (Algae) : OECD Test Guideline 201

\*\* Since the test material is a mixture of isomers, melting point and boiling point will be reported as a range of values.

\*\* Alternative testing proposed by OECD (November 21, 2001, OECD Joint Meeting of the Chemical Committee and Working Party on Chemicals, Pesticides and Biotechnology) may be employed. Alternative tests are OECD Test Guidelines 420, 423 or 425.

#### REFERENCES

NTP Report on the Toxicity Studies of Cresols in F344/N Rats and B6C3F1 Mice. Dennis Dietz, US Department of Health and Humans Services, February, 1992.



## ATTACHMENT 1

Mammalian reproductive/developmental toxicity summaries and genetic toxicity summaries of methyl phenol isomers (o-, m-, and p-cresol)

## CRESOLS ISOMER MAMMALIAN TOXICITY COMPARISON

STUDY NOAEL	o-CRESOL	m-CRESOL	p-CRESOL
Rabbit Oral Gavage Developmental Toxicity: Maternal NOAEL & Effect/Target Organ	5 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes.	5 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes.	5 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes; 15% and 35% mortality in mid- and high- dose vs. 0% in controls.
Rabbit Oral Gavage Developmental Toxicity: Developmental NOAEL & Effect/Target Organ	50 mg/kg/day No embryotoxicity or fetotoxicity. Skeletal variations observed in mid- and high-dose pups	100 mg/kg/day No embryotoxicity or fetotoxicity.	100 mg/kg/day No embryotoxicity or fetotoxicity.
Rat Oral Gavage Developmental Toxicity: Maternal NOAEL & Effect/Target Organ	175 mg/kg/day Hypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 16% mortality.	175 mg/kg/day Hypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 0% mortality.	175 mg/kg/day Hypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 12% mortality.
Rat Oral Gavage Developmental Toxicity: Developmental NOAEL & Effect/Target Organ	175 mg/kg/day No increase in malformations, visceral variations at the high-dose.	450 mg/kg/day No increase in malformations. No increase in variations.	175 mg/kg/day No increase in malformations, skeletal variations at the high-dose.
Two-Generation Reproductive Toxicity In Rats by Oral Gavage: Parental NOAEL & Effect/Target Organ	30 mg/kg/day Transient hypoactivity, audible respiration, ataxia, twitches, tremors, initially decreased food consumption and body weight gain, 52% - 28% mortality across sexes and generations. No lesions specifically noted in organs from F0 and F1 adult necropsy.	<30 mg/kg/day Transient hypoactivity, audible respiration, ataxia, twitches, tremors, initially decreased food consumption and body weight gain, 40% - 12% mortality across sexes and generations. Brain hemorrhage, atrophied seminal vesicle, lung congestion noted at necropsy of F0 but not F1 parents.	30 mg/kg/day Transient hypoactivity, audible respiration, ataxia, twitches, tremors, initially decreased food consumption and body weight gain, 40% - 4% mortality across sexes and generations. Lung congestion noted at necropsy of F0 parents, atrophied seminal vesicle and lung congestion noted at necropsy of F1 parents.
Two-Generation Reproductive Toxicity In Rats by Oral Gavage: Offspring NOAEL & Effect/Target Organ	175 mg/kg/day No gross lesions in F1 or F2 pups.	175 mg/kg/day No gross lesions in F1 or F2 pups.	175 mg/kg/day No gross lesions in F1 or F2 pups.

# SUMMARY OF CRESOLS MUTAGENICITY DATA

<u>ASSAY</u>	<u>TEST SUBSTANCE</u>			
<u>GENE MUTATION</u>	ORTHO	META	PARA	MIXED
SALMONELLA ACTIVATION	-	-	-	-
SALMONELLA NONACTIVATION	-	-	-	-
MOUSE LYMPHOMA ACTIVATION	-	nd	nd	+
MOUSE LYMPHOMA NONACTIVATION	-	nd	nd	nd
*MOUSE LYMPHOMA ACTIVATION	nd	-	-	nd
*MOUSE LYMPHOMA NONACTIVATION	nd	-	-	nd
*SLRL DROSOPHILA	-	nd	-	nd
<u>DNA EFFECTS</u>				
UDS	-	nd	+	+
*HEPATOCYTE UDS	nd	-	nd	nd
<u>CHROMOSOME DAMAGE</u>				
ROOT TIP	+	+	+	nd
SCE ACTIVATION	?	-	-	+
SCE NONACTIVATION	?	-	-	+
*CHO CYTOGENETICS ACTIVATION	+	-	+	nd
*CHO CYTOGENETICS NONACTIVATION	+	-	+	nd
*MOUSE (IN VIVO) CYTOGENETICS	nd	-	nd	nd
*MOUSE DOMINANT LETHAL	-	nd	-	nd
MOUSE MICRONUCLEUS				-
<u>CELL TRANSFORMATION</u>				
BALB/C 3T3 ACTIVATION	-	nd	nd	+
*BALB/C 3T3 ACTIVATION	-	-	nd	nd
*BALB/C 3T3 NONACTIVATION	nd	-	+	nd
C3H10T1/2 ACTIVATION	nd	nd	+	nd
C3H10T1/2 NONACTIVATION	nd	nd	nd	nd

\* ACC PANEL ASSAYS

nd = No Test Data

+ = Positive for Genetic Toxicity

- = Negative for Genetic Toxicity

? = Equivocal Results for Genetic Toxicity

## REFERENCES: ATTACHMENT 1

### Developmental Toxicity and Reproductive Toxicity References:

R. W. Tyl, Unpublished Report Number 51-508: "Developmental Toxicity Evaluation of o-, m-, or p-cresol Administered by Gavage to New Zealand White Rabbits," Bushy Run Research Center, Export, Pa., June 27, 1988.

R. W. Tyl, Unpublished Report Number 51-509: "Developmental Toxicity Evaluation of o-, m-, or p-cresol Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., June 29, 1988.

T. L. Neeper-Bradley and R. W. Tyl, R. W. Tyl, Unpublished Report Number 51-634: "Two Generation Reproduction Study of m-Cresol, Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., February 28, 1989.

T. L. Neeper-Bradley and R. W. Tyl, R. W. Tyl, Unpublished Report Number 51-614: "Two Generation Reproduction Study of o-Cresol, Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., December 19, 1989.

T. L. Neeper-Bradley and R. W. Tyl, R. W. Tyl, Unpublished Report Number 51-512: "Two Generation Reproduction Study of p-Cresol, Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., March 28, 1989.

### Genetic Toxicity References:

IUCLID Data Sheet: o-Cresol CAS Number 95-48-7, European Chemicals Bureau, February 11, 2000.

IUCLID Data Sheet: m-Cresol CAS Number 103-39-4, European Chemicals Bureau, June 19, 1997.

IUCLID Data Sheet: Mixed Cresols CAS Number 1319-77-3, European Chemicals Bureau, March 1, 2001.